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The goals of this research are to delineate basic mechanisms controlling the human circadian clock and to derive practical procedures to rapidly phase-shift human rhythms in real life situations. The focus is on the impact of the interactions between circadian rhythmicity and sleep-wake regulation on endocrine function, metabolism, cardiovascular function, mood and cognition. The studies are designed to approximate real life conditions and examine conditions of circadian misalignment and sleep loss that are relevant to Air Force operations. This effort demonstrated that physical exercise is capable of phase-delaying human rhythms and that daytime exposure to dark may result in rapid phase-advances. We also showed that the subjective discomfort, fatigue, and decreased performance which occur following time shifts (i.e. the "jet lag syndrome") are associated not only with a misalignment of bodily rhythms but also with a prolonged elevation of a hormonal concentration in blood. Recent studies further indicated that partial sleep loss, whether acute or chronic, results in marked alterations of endocrine and metabolic function. These observations challenge the common belief that sleep deprivation affects mood and cognition, but not peripheral physiology, and emphasize the need to develop countermeasures to minimize decrements in both mental and physical function.

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OBJECTIVES AND OVERVIEW OF PROGRESS

The specific aims of this project included:

1. to define the role of exercise intensity and duration in causing phase-shifts of human rhythms;
2. to determine if morning exposure to a single daytime pulse of exercise is capable of phase-advancing human rhythms.

It was planned that the data from studies performed under aims 1 and 2, when combined with our previous observations, would provide a partial human phase-response curve to exercise covering nearly 16 hours of the 24-h cycle. This objective has been reached and the results are summarized in section A below. Section B describes the findings regarding the neuroendocrine effects of daytime versus nighttime exercise that were obtained in the course of these studies. We also performed a detailed analysis of the effects of bright light or exercise exposure on sleepiness and performance which is summarized in section C.

3. to examine the phase-shifting effects of a single daytime pulse of darkness presented at various circadian times. Our findings on the effects of afternoon exposure to dark are described in section D.

4. to carry out studies of conditions that are highly relevant to Air Force operations, i.e. jet lag and sleep loss. Our study of hormonal profiles in the course of adaptation to an 8-hour phase-advance and of the effects of exposure to bright light or pharmacological facilitation of sleep on adaptation to this simulated "jet lag" is included in Section D. Section E summarizes our findings on the metabolic and endocrine effects of total or partial sleep loss. Finally, our studies on the circadian and homeostatic control of mood and cognitive performance are described in Section F.

A total of 26 publications has resulted from this effort.

STUDIES COMPLETED

A. Phase-shifting effects of exercise

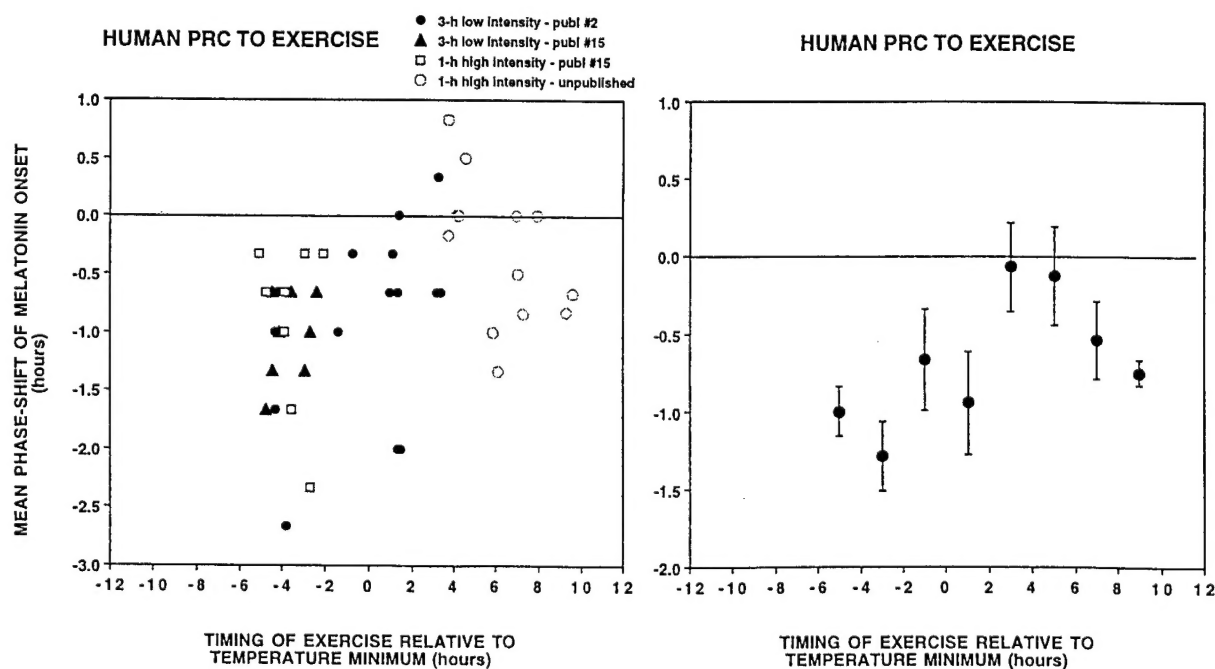
- *The human phase-response curve to exercise*

We have studied a total of 38 normal young subjects who were exposed to sessions of physical exercise at various times of the circadian cycle. In a first study, 17 subjects were studied twice under so-called "constant routine" conditions (i.e. a regimen of constant recumbency, constant dim light (<200 lux) exposure, continuous wakefulness and constant caloric intake under the form of an intravenous glucose infusion), once in the absence of stimulus and once with a 3-h nocturnal exercise session interrupting the constant routine conditions. Phase delays on the order of 1-2 hours were observed when the exercise session occurred 2-5 hours before the timing of the minimum of core body temperature, while smaller phase delays were observed when the exercise session was scheduled around or shortly after the timing of the temperature minimum (publication #2). Our second study was designed to determine the role of intensity and duration of

exercise and included 8 healthy male subjects who were each studied three times in constant routine conditions with no exercise, a 3-h period of low intensity exercise identical to that used in the first study, and a 1-h bout of high intensity exercise. Exercise stimulus was centered at a clock time of 1 am. The results confirmed that a 3-h period of low intensity exercise in this range of circadian times result in phase delays of 1-2 hours and demonstrated that high intensity exercise of 1-h duration, a protocol more compatible with the demands of a real life setting, caused similar phase delays (publication #15). A third study enrolled 13 healthy men and examined the effects of 1-h high intensity exercise in the morning and early afternoon (09-10; 11-12; 13-14; manuscript in preparation). In all three studies, exercise capacity was determined for each individual prior to the study and the intensity of the exercise was tailored to the individual VO_2max . The onsets of the circadian elevations of plasma TSH and melatonin levels were used to determine circadian phase before and after stimulus presentation. The timing of the stimulus relative to endogenous circadian phase was determined a posteriori from the timings of the TSH and melatonin onsets prior to exercise as previously described (publication #1). Figure 1 illustrates the individual data as well as the overall human phase-response curve to exercise delineated by these three studies using the timing of the melatonin onset as marker of circadian phase.

The findings summarized in Figure 1 indicate that the phase-shifting effects of exercise are generally in the delaying direction, except 2 to 5 hours after the minimum of body temperature when, on average, phase-shifts were not significantly different from zero. In our laboratory, in normal 20-30 year old male subjects, the minimum of body temperature under constant routine conditions occurs at $05:00 \pm 85$ min. Thus, based on the data shown in Figure 1, it would be expected that exercise between 6 am and 11 am will have no effect on circadian phase, whereas at all other times of day, exercise (of sufficient duration and intensity) will be associated with a delay of circadian phase, as estimated by the dim light melatonin onset. When all phase-shifts observed in response to nighttime exercise were pooled (publication #15), a significant trend towards greater delays in the earlier part of the night was detected. Ongoing efforts examine the effects of afternoon exposure to 1-h high intensity exercise to complete the human PRC to exercise.

Figure 1

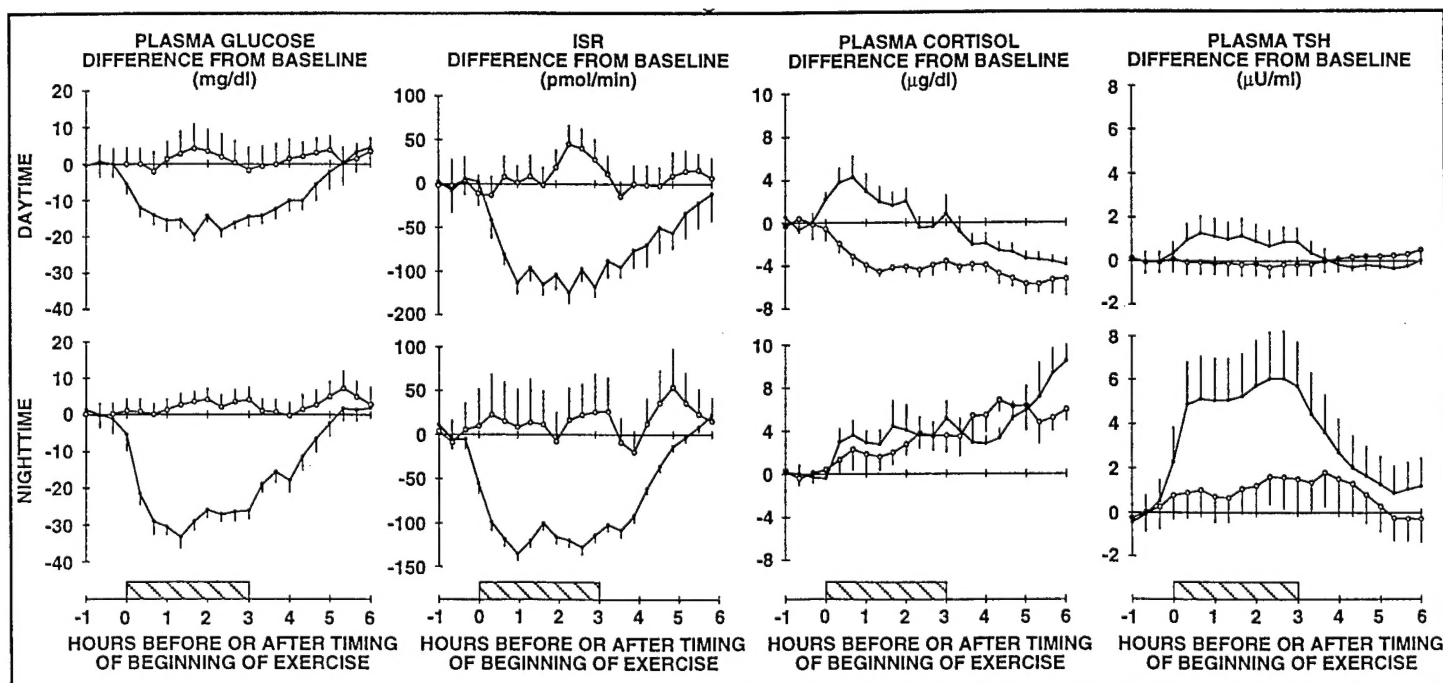


B. Neuroendocrine effects of daytime versus nighttime exercise

Although it is known that glucose metabolism and neuroendocrine secretions affected by exercise (e.g. cortisol, GH and insulin) are markedly modulated by both circadian rhythmicity and sleep, almost all studies on the neuroendocrine and metabolic effects of exercise have been performed in the morning. However, in conditions of jet lag and shift work, exercise often occurs at abnormal times of day. Our studies on the phase-shifting effects of exercise have provided an opportunity to delineate daytime versus nighttime differences in metabolic and neuroendocrine responses to exercise. We compared, in young healthy men, the metabolic and hormonal responses to a 3-hour exercise bout (40-60 % VO_2 max), as compared to continuous bedrest, at two different times of the 24-h cycle period, i.e. around midnight (i.e. at 23:30, near the time of the cortisol nadir), and in the afternoon (i.e. at 14:30, during the decreasing phase of cortisol concentrations). To avoid possible influence of different meal schedules, all subjects remained fasted and received a constant glucose infusion as energy supply. In such conditions, changes in plasma glucose concentrations mainly reflect changes in glucose utilization because glucose production is largely suppressed.

For each measured blood constituent, the baseline level was calculated as the mean of the three values measured during the 60-min period preceding the scheduled period of exercise (or bedrest). The effects of exercise vs rest during the day and during the night were quantified by calculating the area under the curve above (positive area) or below (negative area) the baseline level during the 3-hour exercise or rest period as well as by calculating the maximum difference between the exercise and rest condition. Figure 2 summarizes the major findings of the study.

Figure 2



Mean (+SEM) temporal profiles of plasma glucose (left), insulin secretion rates (ISR, 2nd from left), plasma cortisol (3rd from left) and plasma TSH (right) during exercise (closed symbols) or recumbency (open symbols) during the daytime (top panels) or the nighttime (bottom panels). The timing of the 3-h exercise session is indicated by a dashed bar.

Briefly, there were major daytime versus nighttime differences in the glucose, cortisol and TSH responses to exercise. Decreases in glucose levels (representing primarily increases in glucose utilization) were nearly twofold larger for nighttime exercise than for daytime exercise despite relatively similar rates of insulin secretion. Cortisol elevations in response to exercise were significant in the afternoon only. GH elevations were significant at both times of day and were not influenced by time of day (not shown). Major daytime versus nighttime differences in TSH responses to exercise were observed, indicating that the effects of exercise on TSH levels are much more pronounced when exercise occurs at a time of stimulated TSH secretion (i.e. after the major nocturnal TSH elevation) than at a time of low daytime secretion. Analyses of relationships between decreases in glucose levels and elevations in hormonal concentrations revealed a significant correlation between the drop in glucose and the increase in TSH, suggesting that the metabolic effects of nighttime exercise may be modulated by TSH, a hormone which increases nearly twofold during nocturnal, but not diurnal, sleep deprivation.

These findings indicate that the metabolic and neuroendocrine effects of exercise are likely to be markedly different when exercise occurs at the usual time of day than when it is displaced towards the nighttime period, as may happen in the course of adaptation to jet lag or shift work (publication #18).

C. Effects of bright light or exercise exposure on sleepiness and performance

This study delineated for the first time the temporal relationships between subjective fatigue, neuroendocrine function and a measure of glucose utilization during sleep deprivation (publication #12). Measurements of subjective fatigue (as assessed by the Stanford Sleepiness Scale), cognitive performance (on a digit symbol substitution test and a symbol copying task), body temperature and of the peripheral concentrations of melatonin, thyrotropin (TSH) and cortisol were obtained simultaneously at frequent intervals in 17 normal young subjects submitted to a 43-h period of constant routine conditions, involving continuous wakefulness at bedrest in dim indoor light. Following the completion of a baseline constant routine study, the volunteers participated in two subsequent studies using the same protocol to determine the immediate psychophysiological effects of exposure to a 3-hour pulse of bright light or to a 3-h pulse of physical exercise.

Sleepiness and performance varied in a mirror image, with significant negative correlations. Sleepiness scores were minimal around noon, and then increased at a modest rate throughout the rest of the normal waking period. Staying awake during usual bedtime hours was associated with an acceleration in the rate of increase in sleepiness. When body temperature reached its nadir, a further major increase in sleepiness occurred, in parallel with a pronounced decrease in plasma glucose (reflecting increased glucose utilization). Recovery from maximal sleepiness started when blood glucose levels stopped falling and when significant decreases in cortisol and melatonin concentrations were initiated. Lower levels of subjective sleepiness resumed when glucose concentrations and body temperature had returned to levels similar to those observed prior to sleep deprivation, and melatonin and TSH concentrations had returned to daytime levels. The synchrony of behavioral, neuroendocrine and metabolic changes suggests that circulating hormonal levels could exert modulatory influences on sleepiness

and that metabolic alterations may underlie the sudden increase in fatigue consistently occurring at the end of a night of sleep deprivation.

Effects of bright light or exercise exposure on subjective sleepiness appeared to be critically dependent on the timing of exposure. We were unable to demonstrate significant decreases in sleepiness or increases in performance during light exposure. However, effects of light exposure on SSS were seen following the termination of exposure to light and appeared to persist throughout the day following the night of sleep deprivation. These effects of light exposure were dependent on the timing of light exposure relative to the period of maximal sleepiness. When the light pulse was given in the early part of the night, melatonin levels rebounded to high concentrations in the later part of the night, the offset of nocturnal secretion was delayed and subjective sleepiness during the subsequent day tended to be higher than under baseline conditions. When the light pulse was given during the later part of the night, melatonin levels no longer returned to high concentrations at the end of light exposure, the offset of nocturnal melatonin secretion was therefore advanced and subjective sleepiness during the subsequent day tended to be lower than under baseline conditions. These findings indicate that the later part of the night is the period of choice for the use of light to alleviate sleepiness during conditions involving prolonged sleep deprivation.

The effects of exercise on sleepiness also appeared to be dependent on the timing of exercise exposure relative to the major early morning increase in sleepiness. In subjects who exercised prior to the major early morning increase in sleepiness, exercise did not have any immediate effect on sleepiness scores but tended to increase subjective fatigue throughout the next day. In contrast, in subjects who exercised during peak levels of sleepiness, subjective fatigue appeared partially alleviated during the exercise session, and SSS scores on the following day did not differ from those recorded in the absence of physical activity. These findings indicate that, under controlled laboratory conditions involving dim indoor light conditions, increased physical activity may counteract the major early morning trough of alertness.

D. Hormonal rhythms and sleep during to 8-h advance of light-dark cycle

This study was designed to delineate alterations in 24-h hormonal profiles (TSH, thyroid hormones, melatonin, cortisol) and sleep following an 8-hour advance shift achieved without enforcing prolonged sleep deprivation. The effects of bright light exposure or sleep facilitation with zolpidem were investigated in separate studies performed in the same subjects. Each study involved blood sampling at 20-min intervals for 68 hours and included a baseline period with dim light during waking hours and 23-07 h bedtimes in total darkness. The 8-hour shift was achieved by advancing bedtimes to 15-23 h. The effects of the phase-advance were markedly different for each hormonal system, reflecting differential effects of sleep displacement, circadian misalignment and their interaction, and are therefore the object of 3 separate reports (publication #7, publication #17, one publication in preparation).

- *The "jet lag syndrome" may be associated with an elevation of TSH levels*

Previous studies which had examined perturbations of hormonal patterns during adaptation to real or simulated "jet lag" concurred in demonstrating that the misalignment between the sleep-wake cycle and endogenous circadian rhythmicity was associated with an abnormal synchronization of hormonal events but that mean

hormonal concentrations were not altered. In contrast, the present study demonstrated that, during the two first days following the 8-h advance of the sleep-wake and dark-light cycles, plasma TSH levels increase progressively because daytime sleep fails to inhibit TSH and nighttime wakefulness is associated with large TSH elevations. As a result, in the absence of countermeasure, mean daytime TSH levels may be two- to threefold higher than under baseline conditions. This increase in plasma TSH levels appeared associated with a trend towards a small elevation of T_3 , but not T_4 , levels. Both bright light treatment and pharmacological sleep facilitation can limit the progressive elevation of TSH levels occurring during adaptation to a phase advance but distinct mechanisms underlie their beneficial effects. The effects of bright light are likely to reflect accelerated adaptation of circadian rhythmicity. The study with zolpidem provided no evidence for an effect of hypnotic treatment on circadian phase (publication #7).

- *Phase-shifting effects of daytime exposure to dark pulses*

Analyses of the melatonin profiles indicated that the advance of the dark period from 23-07 to 15-23 resulted in an 1h30-2h advance of the onset of melatonin secretion which appeared within 6 hours after lights out. This phase advance was not limited to the onset of nocturnal secretion but affected the entire profile. The subsequent exposure to dim light or bright light starting at the usual bedtime and extending for the next 16 hours had only modest additional effects on the synchronization of the melatonin onset on the second day after the shift. However, facilitating effects of bright light exposure on the melatonin offset were clearly apparent on the 2nd day after the shift. In contrast, under zolpidem, the phase-shifts of the melatonin onset were smaller than those observed in the absence of treatment.

At least two distinct mechanisms may underlie the unexpected observation of a rapid advance of the melatonin onset after 4-6 hours of scheduled sleep in total darkness starting in the mid afternoon. Since the dim light intensity (± 200 lux) had clear inhibitory effects on nocturnal melatonin levels, it is possible that, under baseline conditions, evening dim light exerted masking effects on the melatonin onset that were eliminated by prolonged exposure to darkness. However, recent studies which have measured the melatonin onset in similar population of subjects but under conditions of lower illumination ($< 10-50$ lux) have consistently reported onset times around 22 h, i.e. similar to those observed under baseline conditions in the present study. Thus, it appears unlikely that the use of dimmer light at baseline would have resulted in a smaller phase-advance of the onset during dark exposure. The fact that the entire melatonin profile was advanced following dark exposure also argues against a simple unmasking effect. An alternative mechanism is that exposure to dark directly affects human circadian phase. Phase-response curves to dark pulses have been described in studies of nocturnal as well as diurnal rodents. The present study provides evidence that exposure to dark may have phase-shifting effects in the human. A role for the associated change in rest-activity state cannot be excluded but is not supported by the present study. Indeed, there were no correlations between any measure of sleep quantity or quality and magnitude of the phase-shift and pharmacological facilitation of sleep by zolpidem was not associated with larger phase-shifts than placebo treatment (publication #17).

- *Pharmacological sleep facilitation exacerbates disturbances of cortisol secretion*

Ongoing analyses of the cortisol profiles have revealed that masking effects of the advanced sleep-wake cycle (i.e. short term inhibition following sleep onset; short term stimulation following awakenings) prevented the derivation of reliable estimations of endogenous circadian phase from the cortisol profiles.

The acrophase of the cortisol waveshape largely failed to adapt to the new schedule, as the total shift achieved on the 2nd day after the 8-h phase advance averaged only 60 min. In contrast, the nadir advanced by more than 3 hours. There were no differences between the dim light, bright light and zolpidem studies for the timing of the acrophase or the nadir. The quiescent period of cortisol secretion was abridged by 2 to 3 hours on the 1st and 2nd day after the shift, as compared to baseline. This failure to suppress cortisol levels for a normal period of time was more pronounced in the zolpidem study, than in the two other studies. Indeed, during the shifted sleep periods treated with zolpidem, cortisol levels were modestly, but significantly, higher than during the dim light and bright light studies. Since we had previously shown that administration of the same dosage of zolpidem at the normal bedtime (i.e. 23 h) has no detectable effects on overnight plasma cortisol levels (19), these findings indicate that the neuroendocrine effects of the drug vary according to time of day.

In summary, in the course of adaptation to advance jet lag, pharmacological sleep facilitation with zolpidem had beneficial effects on sleep quality and limited the elevation of TSH levels, but failed to accelerate the adaptation of circadian phase and exacerbated the disruption of hypothalamo-pituitary-adrenal function (manuscript in preparation).

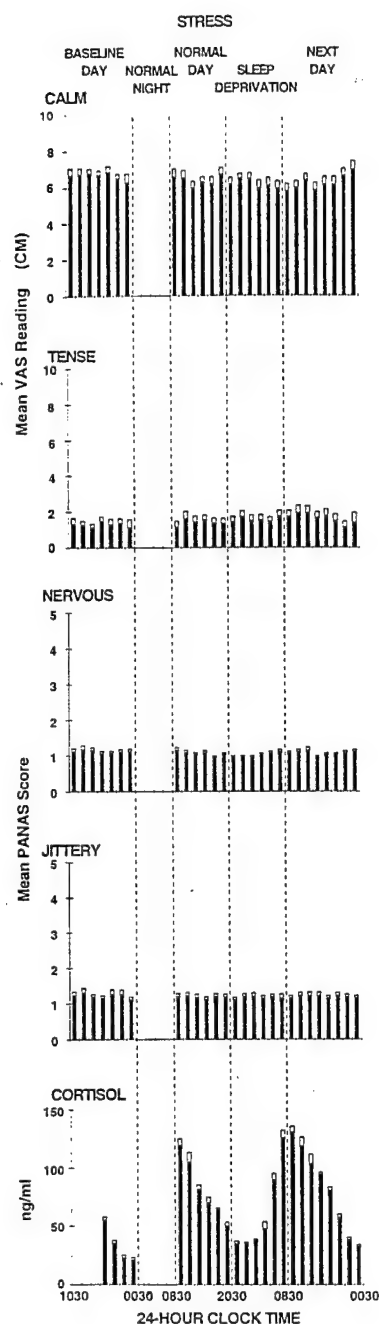
E. Metabolic and endocrine effects of total or partial sleep loss

Sleep curtailment is an increasingly common condition in industrialized societies. Around the clock operations imply chronic partial sleep loss for the large population of shift workers and the repeated occurrence of acute total sleep deprivation for certain key personnel. While the consequences of sleep loss for performance and safety have recently received public attention, little is known about possible adverse effects on health. Indeed, sleep loss is generally thought to affect behavioral, rather than physiological, function. During the previous grant period, we examined the effects of acute partial or total sleep deprivation on the profile of cortisol levels (Publication #14) and initiated a study on the effects of partial sleep loss for several consecutive days (i.e. building a "sleep debt") on hormonal, metabolic and cardiovascular function as well as mood and cognitive performance (Abstract # 13).

- Effects of sleep loss on alterations of the corticotropic axis

Plasma cortisol profiles were determined during a 32-h period in normal young non-obese subjects submitted to three different protocols: normal sleep schedule (n=9; 23-07); partial sleep deprivation (n=7; sleep: 04-08); total sleep deprivation (n=17). The subjects remained recumbent throughout the study. In the absence of sleep deprivation, cortisol levels over the time period 18-23 were similar on the two consecutive days of the study. In contrast, both partial sleep loss and total sleep loss were followed by significant increases of cortisol levels over the 18-23 period on the 2nd as compared to the 1st day. Thus, sleep loss appeared to delay the recovery of the

hypothalamo-pituitary-adrenal axis from early morning circadian stimulation, resulting in elevated evening cortisol levels. This is likely to involve an alteration in negative glucocorticoid feedback regulation. We hypothesize that sleep loss could thus affect the rate of recovery from stress, i.e. the resiliency of the stress response.



We have recently confirmed these observations in an independent group of 13 young non-obese healthy subjects who underwent total sleep deprivation under the same experimental conditions. These subjects were asked to complete a set of visual analog scales (VAS) designed to measure vigor and affect as well as the Positive Affect and Negative Affect Scale (PANAS) at hourly intervals. Both these instruments include subjective measures of stress. The VAS for mood include a scale for "calm" and a scale for "tense". The PANAS requests a score on the adjectives "nervous" and "jittery". Fig. 3 illustrates the cortisol profiles as well as the scores on these four subjective measures of "stress". Interestingly, while the volunteers did not rate the sleep deprivation as stressful on any of the four scales, evening cortisol levels were clearly elevated following sleep deprivation.

Figure 3

Mean (and SEM in open bars) scores on four subjective assessments of stress and cortisol levels at 2-h intervals during a normal day and during 40 hrs of continuous wakefulness.

F. Effects of circadian and sleep-wake homeostasis on mood and cognition

Studies using experimental designs dissociating the sleep-wake cycle from circadian rhythmicity have demonstrated that sleepiness is a function of the duration of prior wakefulness as well as a function of time of day. Self-assessments of mood and performance on simple repetitive tasks are also influenced by circadian rhythmicity and

sleep-wake homeostasis. We took advantage of our "constant routine studies" (performed to derive the human phase-response curve to exercise) to further delineate examine the relationship of sleepiness to mood and cognitive performance using a novel battery of tests, the Harvard Cognitive Performance Battery (HCPB; developed by S. Kosslyn, Harvard University) and a more sophisticated instrument for mood assessment, the Positive and Negative Affect Scale (PANAS). Unlike previous batteries of performance tests, the HCPB measures performance in a range of well-defined cognitive systems that have been mapped by positron emission topography techniques to specific brain regions and includes four tasks, which will be referred to as "logical reasoning", "mental rotation", "vigilance" and "perceptual cueing task" (described in detail in section 5.4). In addition, standard measures used in previous studies (Stanford Sleepiness Scale, VAS scales of mood and vigor, digit symbol substitution task) were also obtained simultaneously at frequent intervals in normal young subjects submitted to a 40-h period of constant routine conditions.

The results are summarized in Table 1 and provided a number of novel insights into the homeostatic and/or circadian control of mood and cognition. In particular, the use of the PANAS demonstrated that positive affect, but not negative affect, is modulated by circadian rhythmicity. An effect of sleep-wake homeostasis on mood could not be detected with the simple VAS scale but the use of the PANAS instrument clearly evidenced an effect of duration of prior wakefulness on positive affect. Remarkably, certain types of cognitive performance, i.e. mental rotation and - to a lesser extent - logical reasoning, appear relatively unaffected by either circadian rhythmicity or sleep-wake homeostasis whereas highly significant effect of both processes were demonstrated for the vigilance task and the perceptual cueing task. Effect size analysis indicated that deleterious effects of sleep deprivation on performance were largest for the throughput (i.e. number of correct answers per unit of time) of the vigilance task (two manuscripts in preparation).

Table 1: Circadian and homeostatic modulation of sleepiness, mood and performance.

	CIRCADIAN	HOMEOSTATIC	EFFECT SIZE
SUBJECTIVE SLEEPINESS			
Stanford Sleepiness Scale	P < 0.001	P < 0.005	3.3
Global Vigor	P < 0.05	P < 0.05	1.9
SUBJECTIVE MEASURES OF MOOD			
Global Affect	P < 0.05	P < 0.05	0.5
Positive Affect	P < 0.001	P < 0.05	0.8
Negative Affect	N/S	N/S	0.1
PERFORMANCE ON THE HCPB			
Vigilance task			
reaction time all stimuli	P < 0.005	P < 0.01	1.5
throughput	P < 0.01	P < 0.005	1.8
Perceptual Cueing task			
reaction time cue valid	P < 0.005	P < 0.05	1.7
reaction time all stimuli	P < 0.06	P < 0.01	1.5
Logical Reasoning task			
reaction time	P < 0.05	N/S	0.8
throughput	N/S	N/S	-
Mental Rotation task			
reaction time	N/S	N/S	-
% error	N/S	N/S	-

PERSONNEL SUPPORTED

Eve Van Cauter, Ph.D.	Research Associate (Professor)
Samuel Refetoff, M.D.	Professor
Rachel Leproult, B.S.	Data manager
Georges Copinschi, M.D.	Professor
George Haake	Technician
Sonya Cespedes	Technician
Orfeu Buxton	graduate student
Ulrich Hirschfeld	graduate student

PUBLICATIONS

1. Van Cauter E, Sturis J, Byrne MM, Blackman JD, Leproult R, Gilad O, L'Hermite-Balériaux M, Refetoff S, Turek FW, Van Reeth O. Demonstration of rapid light-induced advances and delays of the human circadian clock using hormonal phase markers. *Am J Physiol: Endocrinology and Metabolism*, 266: E953-E963, 1994
2. Van Reeth O, Sturis J, Byrne MM, Blackman JD, L'Hermite-Balériaux M, Leproult R, Oliner C, Refetoff S, Turek FW, Van Cauter E. Nocturnal exercise phase delays the circadian rhythms of melatonin and thyrotropin secretion in normal men. *Am J Physiol: Endocrinology and Metabolism*, 266: E964-E974, 1994
3. Copinschi G, Akseki E, Moreno-Reyes R, Leproult R, L'Hermite-Balériaux M, Caufriez A, Vertongen F, Van Cauter E. Effects of bedtime administration of zolpidem on circadian and sleep-related hormonal profiles in normal women. *Sleep*, 18: 417-424, 1995.
4. Kessler Cella L, Van Cauter E, Schoeller DA. Diurnal rhythmicity of human cholesterol synthesis: Normal pattern and adaptation to simulated "jet lag". *Am J Physiology (Endocrinology and Metabolism)*; 269: E489-E498, 1995.
5. Kessler Cella L, Van Cauter E, Schoeller DA. Effect of meal timing on the diurnal rhythm of human cholesterol synthesis. *Am J Physiology (Endocrinology and Metabolism)*; 269: E878-E883, 1995.
6. Plat L, Byrne MM, Sturis J, Polonsky KS, Mockel J, Fery F, Van Cauter E. Effects of morning cortisol elevation on insulin secretion and glucose regulation in man. *Am J Physiology (Endocrinology and Metabolism)* 270: E36-E42, 1996.
7. Hirschfeld U, Moreno-Reyes R, Akseki E, L'Hermite-Balériaux M, Leproult R, Copinschi G, Van Cauter E. Progressive elevation of plasma thyrotropin during adaptation to simulated jet lag: Effects of treatment with bright light or zolpidem. *J Clin Endocrinol Metab* 81: 3270-3277, 1996.
8. Biston P, Van Cauter E, Ofek G, Linkowski P, Polonsky KS, Degaute JP. Diurnal variations in cardiovascular function and glucose regulation in normal man. *Hypertension*, 28: 863-871, 1996.

9. Frank SA, Roland DC, Sturis J, Byrne MM, Refetoff S, Polonsky KS, Van Cauter E. Effects of aging on glucose regulation during wakefulness and sleep. *Am J Physiology (Endocrinology and Metabolism)*; 269: E1006-E1016, 1995.
10. Van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *J Clin Endocrinol Metab*, 81:2468-2473, 1996.
11. Scheen AJ, Byrne MM, Plat L, Leproult R, Van Cauter E. Relationships between sleep quality and glucose regulation in normal man. *Am J Physiol* 271: E261-E270, 1996.
12. Leproult R, Van Reeth O, Byrne MM, Sturis J, Van Cauter E. Sleepiness, performance and neuroendocrine function during sleep deprivation: Effects of exposure to bright light or exercise. *J Biol Rhythms* 12: 245-258, 1997.
13. Van Cauter E, Plat L, Scharf MB, Leproult R, Cespedes S, L'Hermite-Balériaux M, Copinschi G. Simultaneous stimulation of slow-wave sleep and growth hormone by gamma-hydroxybutyrate in normal young men. *J Clin Invest* 100: 745-753, 1997.
14. Leproult R, Copinschi G, Buxton O, Van Cauter E. Sleep loss results in an elevation of cortisol levels the next evening. *Sleep* 20: 865-870, 1997.
15. Buxton OM, Frank SA, L'Hermite-Balériaux M, Leproult R, Turek FW, Van Cauter E. Roles of intensity and duration of exercise in causing phase delays of human circadian rhythms. *Am J Physiol (Endocrinology and Metabolism)*, 273: E536-E542, 1997.
16. Buxton OM, Hirschfeld U, L'Hermite-Balériaux M, Van Cauter E. Acute and delayed effects of exercise on human melatonin secretion. *J Biol Rhythms*, 12: 568-574, 1997.
17. Moreno-Reyes R, Akseki E, L'Hermite-Balériaux M, Hirschfeld U, Leproult R, Caufriez A, Copinschi G, and Van Cauter E. Adaptation of the 24-h melatonin profile to simulated jet lag: Effects of dark, bright light and pharmacological sleep facilitation. *Am J Physiol*, accepted pending revisions, 1998.
18. Scheen AJ, Buxton OM, Jison M, Van Reeth O, Leproult R, L'Hermite-Balériaux M, Van Cauter E. Effects of exercise on neuroendocrine secretions and glucose regulation at different times of day. *Am J Physiol*, accepted pending revisions, 1998.

Review articles and textbook chapters

19. Van Cauter E, Turek FW. Endocrine and other biological rhythms, In: *Endocrinology*, LJ DeGroot (ed), 3rd edition, W.B. Saunders, Philadelphia, 1994, pp 2487-2548.
20. Turek FW, Van Cauter E. Rhythms in Reproduction. In: *The Physiology of Reproduction*, E. Knobil and J.D. Neill (eds), 2nd edition, Raven Press Ltd, New York, 1994, 487-540.

21. Copinschi G, Van Cauter E. Effects of aging on modulation of hormonal secretions by sleep and circadian rhythmicity. *Hormone Research*, 43:20-24, 1995.
22. Copinschi G, Van Cauter E. Pituitary hormone secretion in aging: roles of circadian rhythmicity and sleep. *Europ J Endocrinol* (editorial), 131:441-442, 1994.
23. Van Cauter E. Hormones and Sleep. In: *The Pharmacology of Sleep*, A. Kales (ed), *Handbook of Experimental Pharmacology*, vol. 116, p279-306, Springer-Verlag, Berlin, 1995.
24. Sturis J, Van Cauter E. Techniques for assessing ultradian rhythms in hormonal secretion. In: *Methods in Neurosciences*, vol 28, JD Veldhuis and ML Johnson (eds), Academic Press, San Diego, CA, 139-155, 1995.
25. Van Cauter E, Spiegel K. Hormones and metabolism during sleep. In: *Sleep Science: Integrating Basic research and Clinical Practice*. Karger Monographs in Clinical Neuroscience. W.J. Schwartz (ed), p 144-174, 1997.
26. Van Cauter E, Polonsky KS, Scheen AJ. Roles of circadian rhythmicity and sleep in human glucose regulation. *Endocr Rev* 18: 716-738, 1997.

Abstracts

Plat L, Fery F, Mockel J, Van Cauter E. Evidence for a role of the morning cortisol elevation in causing the diurnal variation of insulin secretion. 1994 Meeting of the ADA, Diabetes 43 (suppl 1): 254a.

Moreno-Reyes R, Akseki E, L'Hermite-Balériaux M, Leproult R, Caufriez A, Vertongen F, Copinschi G, Van Cauter E. Effects of the imidazopyridine hypnotic, zolpidem, taken at bedtime, on nocturnal hormonal profiles in normal women. 76th Annual Meeting of the Endocrine Society, abstract #60, Anaheim, CA, 1994.

Leproult R, Van Reeth O, Byrne MM, Sturis J, Van Cauter E. Effects of exposure to light or exercise on sleepiness and performance during constant routine conditions. IVth Meeting of the Society for Research on Biological Rhythms, Jacksonville, FL, 1994, abstract #109.

Hirschfeld U, Leproult R, Moreno-Reyes R, Kerkhofs M, Akseki E, Copinschi G, Van Cauter E. Bright Light is More Efficacious than Zolpidem in Treating an 8-Hour Advance of the Sleep-Wake Cycle. 9th Annual Meeting of the Associated Professional Sleep Societies, May 30-June 4, Nashville TN, 1995, abstract # 112.

Plat L, Byrne M, Van Reeth O, Van Cauter E, Scheen A. Relationships Between Sleep Quality and Glucose Regulation in Normal Man. 9th Annual Meeting of the Associated Professional Sleep Societies, May 30-June 4, Nashville TN, 1995, abstract # 090.

Hirschfeld U, Moreno-Reyes R, Leproult R, L'Hermite-Balériaux M, Van Cauter E,

Copinschi G. Progressive elevation of plasma TSH during adaptation to simulated jet lag: Effects of treatment with bright light or zolpidem. 1995 Meeting of the Endocrine Society, June 14-17, Washington DC, abstract # 394

Buxton O, Frank S, L'Hermite- Balériaux M, Leproult R, Turek F, Van Cauter E. Roles of Intensity and Duration of Nocturnal Exercise in Phase Delaying Human Circadian Rhythms of Plasma Thyrotropin and Melatonin Secretion. 5th Meeting of the Society for Research on Biological Rhythms, May 8-12, Jacksonville FL, 1996, abstract # 11.

Leproult R, Buxton O, Van Cauter E. Nocturnal sleep deprivation results in an elevation of cortisol levels the next evening. International Congress of Endocrinology, June 12-15, San Francisco, 1996, abstr #P2-422.

Hofmann E, Hochner I, Van Cauter E. Falling asleep alters the glucose and insulin responses to an intravenous glucose tolerance test. International Congress of Endocrinology, June 12-15, San Francisco, 1996, abstr # P3-889.

Plat L, Féry F, L'Hermite M, Mockel J, Van Cauter E. Metabolic effects of short-term physiological elevations of plasma cortisol are more pronounced in the evening than in the morning. 56th meeting of the American Diabetes Association, June 9-12, San Francisco, 1996, abstr # 355.

Bajramovic S, Van Cauter E. Diurnal variations in beta-cell responsiveness to glucose in normal subjects. 56th meeting of the American Diabetes Association, June 9-12, San Francisco, 1996, abstr # 578.

Colecchia E, Berardi A, Hirschfeld U, Kosslyn S, Leproult R, Levin T, Riffle A, Van Cauter E. Mood Across 40 Hours of Continuous Wakefulness. 11th Annual Meeting of the Associated Professional Sleep Societies, June 10-15, San Francisco CA, 1997, abstract # 587.

Spiegel K, Hobson A, Van Cauter E. A Sleep Debt Study. 11th Annual Meeting of the Associated Professional Sleep Societies, June 10-15, San Francisco CA, 1997, abstract # 216.

INTERACTIONS/TRANSITIONS

Participation at meetings, conferences and seminars.

Invited speaker, 1995 National Cooperative Growth Study (NCGS) Investigators Meeting, October 12-15, 1995, New York City, NY

Symposium Chair and Speaker, 1995 Meeting of the Gerontological Society of America, November 15-19, 1995, Los Angeles, CA

Speaker, Advances in Sleep Medicine Winter Meeting, Aspen, February 17-20, 1996

Invited speaker, Servier Workshop on "Melatonin receptors: New targets for a novel therapeutical agent ?", Barcelona, Spain, March 31 -April 2, 1996.

Invited symposium speaker, 5th meeting of the Society for Research on Biological Rhythms, symposium on "Practical circadian biology in the clinic and the workplace", Jacksonville, FL, May 8-12, 1996.

Invited Symposium speaker, International Congress of Endocrinology, symposium on "Biological pulsatility", San Francisco, Ca, June 12-16, 1996.

Organizer, Symposium on "Hormones and Sleep", 13th European Sleep Congress, Brussels, Belgium, June 16-21, 1996.

Invited speaker, Workshop on "The Neuroscience and endocrinology of fibromyalgia", National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, July 16-17, 1996.

Invited speaker, Workshop on "Melatonin and Sleep", National Institute on Aging, NIH, Bethesda, August 12-13, 1996.

Invited speaker, Symposium on "Modernization of shift work, police scheduling, and resource allocation", Justice Research Institute, Chicago, Il, Sept 26-28, 1996.

Invited symposium speaker, XXVIIIth Annual Meeting of the International Society of Psychoneuroendocrinology, San Francisco, CA, July 26-30, 1997

Speaker, Air Force Office of Scientific Research Chronobiology Program Review, US Air Force Academy, Colorado Springs (Co), September 18-20, 1997.

Speaker, Belgian Association for the Study of Sleep, International Autumn meeting on "Sleep Disorders in the Elderly", Brussels, Belgium, October 18, 1997.

Speaker, Société française de Pharmacologie, IIème Séminaire Annuel "Mélatonine, des modèles expérimentaux aux perspectives cliniques", Vaux de Cernay, France, 27-29 November 1997.

Consultative and advisory functions

Merck Research Laboratories, research on growth hormone secretagogues, 1995-1996

Mental Health Clinical Research Center for the Study of Affective Disorders, University of Pittsburgh Medical Center (Dr. D.J. Kupfer) - 1995-1996

Institut de Recherches Internationales Servier (Paris, France), research on melatonin agonists and antagonists, 1995-1996

Reviewer for scientific publications, including:

Sleep

The Journal of Endocrinological Investigation

The American Journal of Physiology

Endocrinology

Neuroendocrinology
 Neuropsychobiology
 Biological Psychiatry
 Psychoneuroendocrinology
 Life Sciences
 Journal of Biological Rhythms
 Journal of Clinical Endocrinology and Metabolism
 Journal of Clinical Investigation
 New England Journal of Medicine

Member of the Advisory Board of the Journal of Biological Rhythms
 Member of the Editorial Board of the Journal of Clinical Endocrinology and Metabolism.

HONORS and AWARDS - Eve Van Cauter, Ph.D. - Principal Investigator

- 1985 Award of the Robert Wallegem Prize for medical research
- 1986 Co-recipient of the Hoechst Belgium Prize for research in
 biological psychiatry (with Dr. Linkowski)
- 1989 Belgian Endocrine Society Award lecture
- 1989 Prize of the 50th Anniversary of the Foundation Soroptimist
 International, Belgium (\$10,000)
- 1992 Elected Secretary of the Society for Research on Biological Rhythms
- 1993 invited member of the MacArthur Foundation Research Network on
 Mind-Body Interactions
- 1994 Chairman of the Scientific Program of the 4th Meeting of the
 Society for Research on Biological Rhythms
- 1995 Lundbeck Prize Belgium (with Drs. Linkowski and Kerkhofs)
- 1995 Member of the Editorial Board of the Journal of Clinical Endocrinology and
 Metabolism
- 1996 appointed to the Committee on Biopsychology, University of Chicago